## REMARKS

Claims 1-8 appear in this application for the Examiner's review and consideration. Claims 9-30 have been withdrawn. Applicants reserve the right to pursue the subject matter of the withdrawn claims in a divisional application.

Rejections under 35 U.S.C. § 102 (b)

Claims 1-8 were rejected under 35 U.S.C. § 102 (b) as allegedly anticipated by Leppert, which the Examiner cites as Nowotory, 51(3), 31-38, 1996, hereinafter referenced as "Leppert". While Applicants respectfully point out that Leppert has a publication date of October 18, 2001, Applicants also respectfully traverse this rejection.

Leppert discloses the results of a study whose aim was the assessment of both the analgesic efficacy and side effects of tramadol and morphine, and the quality of life in cancer patients, and the establishment of equianalgesic doses of oral tramadol and morphine. Patients in the tramadol study group received drops or capsules of immediate release tramadol for the first 7 days. The immediate release tramadol was administered every 4 hours, with a break during the night, the dose administered prior to sleep was increased by 50%. The starting doses were 25-50 mg of tramadol. *See*, Leppert, pp. 257, 259.

After the initial 7 day treatment with immediate release tramadol, if satisfactory pain control was achieved, patients were treated were treated with controlled release analgesics. Patients in the tramadol group received daily doses of 150 – 600 mg of tramadol. Treatment with controlled release tramadol lasted 28 days, and the total trial time was 35 days. If breakthrough pain occurred during the controlled release treatments, immediate release dosages of 10 – 25% of the daily dosage of controlled release tramadol were administered. *See*, Leppert, p. 259.

Leppert neither discloses nor teaches a titration dosage regimen for administering tramadol in a controlled release dosage form once a day. Instead Leppert discloses a study wherein patients were initially administered immediate release tramadol for a period of 7 days, followed by daily doses of from 150 mg to 600 mg of controlled release tramadol for 28 days. Nowhere does Leppert disclose or teach that the amount of tramadol administered in controlled release dosage form be titrated from a dosage of from about 75 mg to about 125 mg for about 4 to about 10 days, then about 175 mg to about 225 mg for about 4 to about 10 days, then about 275 mg to about 325 mg for at least 1 day thereafter, as is disclosed and

claimed in the present invention. In fact, the Examiner explicitly acknowledges this fact at page 3 of the September 18, 2005 Office Action, stating "Leppert does not spell out the exact doses for the exact periods indicated in claim 1 (and its dependent claims 2-8)."

Anticipation under 35 U.S.C. § 102 requires that each and every element of the invention defined in the claim must be met in a single prior art reference. MPEP § 2131; *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Although the use of additional references to confirm the contents of an allegedly anticipating reference is permitted, anticipation does not permit an additional reference to supply a missing claim limitation. *Teleflex, Inc. v. Ficosa North American Corp.*, 299 F.3d 1313 (Fed. Cir. 2002). In addition, to anticipate a claim, a single reference must disclose the claimed invention with sufficient clarity to prove its existence in the prior art, and must disclose every element of the challenged claim. *Motorola Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997); *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 231 USPQ 160 (Fed. Cir. 1986). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). An anticipatory reference must also enable one of ordinary skill in the art as to the claimed subject matter.

As the Examiner has acknowledged, Leppert does not disclose a titration dosage regimen for administering tramadol to a patient comprising administering from about 75 mg to about 125 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 175 mg to about 225 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 275 mg to about 325 mg of tramadol in a controlled release dosage form once a day for at least 1 day thereafter.

Accordingly, Applicants respectfully submit that Leppert fails to teach or suggest each and every element of the invention defined in the claims of the present invention, and, therefore, does not anticipate the present claims under 35 U.S.C. § 102 (b). Applicants respectfully submit that the Examiner's rejection of claims 1-8 under 35 U.S.C. § 102 (b) as allegedly anticipated by Leppert has been overcome, and should be withdrawn.

Rejections under 35 U.S.C. § 103 (a)

Claims 1-8 were also rejected under 35 U.S.C. § 103 (a) as allegedly obvious in light of Leppert. Applicants respectfully traverse this rejection.

As discussed above, Leppert discloses a study wherein patients were initially administered immediate release tramadol for a period of 7 days, followed by daily doses of from 150 mg to 600 mg of controlled release tramadol for 28 days. Further, Leppert discloses that, during the controlled release therapy phase of the study, if breakthrough pain was experienced, immediate release dosages of 10 – 25% of the daily dosage of controlled release tramadol were administered. *See*, Leppert, p. 259.

In contrast, the present invention discloses and claims a titration dosage regimen for administering tramadol to a patient comprising administering from about 75 mg to about 125 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 175 mg to about 225 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 275 mg to about 325 mg of tramadol in a controlled release dosage form once a day for at least 1 day thereafter. As disclosed in the present invention, this titration dosing regimen was shown to provide significant reduction of adverse side effects compared to other dosing regimens which used higher initial dosing strengths of tramadol. Accordingly, increased tolerance of the treatment regimen, and improved patient compliance would be likely results of use of the presently claimed dosing regimen.

Applicants respectfully submit that Leppert neither discloses nor suggests a dosing regimen wherein a controlled release tramadol dosage form is administered to a patient at an initial low dosage level for a number of days, followed by administration of an increased level of controlled release tramadol dosage form for a subsequent number of days, followed by a second increased level of controlled release tramadol dosage form for a subsequent number of days. Leppert discloses only that the daily dosage level of controlled release tramadol is 150 mg to 600 mg. Leppert discloses neither the initial nor the final dosage level of controlled release tramadol. Further, Leppert neither discloses nor suggests that any change to the dosage level of controlled release tramadol is made during the 28 day period of the study. In particular, Leppert neither discloses nor suggests that the controlled release tramadol be administered at an initial low dosage level for a defined number of days, followed by administration of an increased level of controlled release tramadol dosage form for a subsequent defined number of days, followed by a second increased level of controlled

release tramadol dosage form for a subsequent defined number of days, as is taught in the present invention.

In addition, the lowest dosage level of controlled release tramadol disclosed in Leppert is 150 mg. In contrast, the initial dosage level of controlled release tramadol disclosed and recited in the present invention is from about 75 mg to about 125 mg for from about 4 to about 10 days. Accordingly, the initial dosage level of controlled release tramadol disclosed and recited in the present invention can be half that of the lowest dosage level required by Leppert for the second phase of its study. In fact, Leppert states "[t]o enter the second part of the study, patients had to receive daily doses of tramadol of 150-600 mg. *See*, Leppert, p. 259 (emphasis added). Applicants therefore submit that the initial dosage level of from about 75 mg to about 125 mg of controlled release tramadol disclosed and recited in the present invention is not obvious in light of Leppert's requirement of a daily dosage of 150 mg to 600 mg.

A finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art , (3) the difference between the claimed subject matter and the prior art, and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1, 17 (1966). Therefore, obviousness inquiries require determining whether the prior art suggests the claimed invention and whether that prior art would have indicated a reasonable expectation of success to one of ordinary skill in the art. *In re O'Farrell*, 853 F.2d 894, 902-903, 7 USPQ2d 1673, 1680-1681 (Fed. Cir. 1988). Furthermore, "the prior art must teach or suggest all of the claim limitations." MPEP §§2142, 2143, emphasis added.

The Examiner has the burden of establishing a *prima facie* case of obviousness by proving three elements: (1) a particular reference (or combined references) must suggest or teach all the limitations of the challenged claim, (2) a suggestion or motivation from the prior art to modify or combine the reference teachings, and (3) a reasonable expectation of success must exist from the prior art. MPEP §§2142, 2143, citing *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Care must be exercised not to use the applicant's disclosure to fill in the gaps of the prior art. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Applicants respectfully submit that Leppert fails to teach or suggest all of the claim limitations, as discussed in detail above. In fact, Applicants submit that Leppert contains no

teaching or suggestion that any change to the dosage level of controlled release tramadol be made, other than to administer an immediate release form of the drug in the event of breakthrough pain. In particular, Leppert neither discloses nor suggests that the controlled release tramadol be administered at an initial low dosage level for a number of days, followed by administration of an increased level of controlled release tramadol dosage form for a subsequent number of days, followed by a second increased level of controlled release tramadol dosage form for a subsequent number of days, as is taught in the present invention. Applicants respectfully submit that there is no suggestion or motivation from the prior art to modify the teachings of Leppert to include, *inter alia*, a titration dosage regimen for administering tramadol to a patient comprising administering from about 75 mg to about 125 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 175 mg to about 225 mg of tramadol in a controlled release dosage form once a day for about 4 to about 10 days, then about 275 mg to about 325 mg of tramadol in a controlled release dosage form once a day for at least 1 day thereafter.

Accordingly, Leppert does not render the present claims, each of which require a titration dosing regimen of controlled release tramadol, obvious under 35 U.S.C. § 103. Applicants respectfully submit that in view of the remarks above, the Examiner's rejection over Leppert has been overcome, and should be withdrawn.

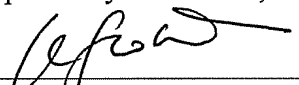
Conclusion

In light of the above remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (212) 692-1086, if a telephone call could help resolve any remaining items.

It is respectfully requested that the above amendment and remarks be entered into the file of the application. No fee beyond that for the extension of time is believed to be due for this amendment. However, the Commissioner is hereby authorized to charge any required fee to Duane Morris Deposit Account No. 04-1679.

Respectfully submitted,

Date: February 19, 2008



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